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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/649,952	08/28/2003	Kenju Miura	58777.000013	7207

21967 7590 06/07/2005

HUNTON & WILLIAMS LLP
INTELLECTUAL PROPERTY DEPARTMENT
1900 K STREET, N.W.
SUITE 1200
WASHINGTON, DC 20006-1109

EXAMINER	
BUNNER, BRIDGET E	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 06/07/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/649,952	MIURA ET AL.	
	Examiner	Art Unit	
	Bridget E. Bunner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 March 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 August 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/10/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

20001

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendment of 29 March 2005 has been entered in full. Claims 1-15 are cancelled. Claims 19-20 are amended. Claims 21-34 are added.

Election/Restrictions

Applicant's election with traverse of Group II, claims 16-18, drawn to a method of promoting growth, differentiation of hematopoietic stem cells comprising administering Cofilin, in the reply filed on 29 March 2005 is acknowledged. The traversal is on the ground(s) that the restriction requirement is improper because is does not establish that searching all the inventions would constitute an undue burden on the Patent Office. Applicant argues that it would not constitute an undue burden to examine the inventions of Groups II and III together. Applicant contends that the search within each of Groups II and III would overlap because Groups II and III both encompass methods involving administering or using at least one promoter of growth, differentiation of hematopoietic stem cells wherein at least one promoter contains Cofilin as an active ingredient. Applicant adds that a search of new claim 34, which requires that the promoter can be used in regenerative medicine, would necessarily include the search of the administration of the promoter *in vivo* or *ex vivo*. Applicant's arguments have been found to be persuasive in part. The methods of Groups II and III are rejoined.

Claims 16-34 are under consideration in the instant application.

Sequence Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2).

Specifically, the sequences disclosed in Figures 1, 2, and 3 are not accompanied by the required reference to the relevant sequence identifiers. Additionally, the specification discloses partial amino acid sequences at page 29 that are not accompanied by the required reference to the relevant sequence identifiers. This application fails to comply with the requirements of 37 CFR 1.821 through 1.825. Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825).

Information Disclosure Statement

The information disclosure statement filed 10 March 2004 fails to comply with 37 CFR 1.98(a)(3) because it does not include a concise explanation of the relevance, as it is presently understood by the individual designated in 37 CFR 1.56(c) most knowledgeable about the content of the information, of each patent listed that is not in the English language. It has been placed in the application file, but the information referred to therein has not been considered. Specifically, JP 08510998T2; Igaku, J. March 1994; Igaku, J. May 1994; and Moriyama et al. 1999 are in Japanese and do not have a concise explanation of their relevance in English.

Specification

1. The disclosure is objected to because of the following informalities:

2. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (See for example, page 28, [93]). Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

3. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The following title is suggested: "METHOD OF PROMOTING THE GROWTH AND DIFFERENTIATION OF HEMATOPOIETIC STEM AND PROGENITOR CELLS BY NON-MUSCLE TYPE COFILIN".

Appropriate correction is required.

Claim Objections

4. Claims 16-17, 21-25, and 32 are objected to because of the following informalities:

4a. Claims 16-17, 21-25, and 32 are missing a word in the phrase "growth, differentiation of hematopoietic stem cells...". (Please note that this objection can be overcome by amending the claims to recite, for example, "growth and differentiation of hematopoietic stem cells...".)

Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

5. Claims 19-20 and 34 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 112, first paragraph

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 16-34 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for: (1) a method of promoting the growth of hematopoietic stem cells and hematopoietic progenitor cells *in vitro* or *ex vivo* comprising administering human non-muscle type Cofilin of SEQ ID NO: 1 to hematopoietic stem cells or hematopoietic progenitor cells *in vitro* or *ex vivo* to promote growth and (2) a method of promoting the differentiation of hematopoietic stem cells and hematopoietic progenitor cells *in vitro* or *ex vivo* comprising administering human non-muscle type Cofilin of SEQ ID NO: 1 and one or more cytokines to hematopoietic stem cells or hematopoietic progenitor cells *in vitro* or *ex vivo* to promote differentiation, *does not* reasonably provide enablement for a method of treating a disease or promoting growth, differentiation of hematopoietic stem cells, hematopoietic progenitor cells said method comprising administering at least one promoter of growth, differentiation of hematopoietic stem cells, hematopoietic progenitor cells, wherein said at least one promoter contains Cofilin as an active ingredient. The specification also does not reasonably provide enablement for a method of regenerative medicine or expanding hematopoietic stem cells *ex vivo* by using at least one promoter of growth, differentiation of hematopoietic stem cells, hematopoietic progenitor cells, wherein said at least one promoter contains Cofilin as an active ingredient. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims also recite that the Cofilin has the amino acid sequence depicted by SEQ ID NO: 1 or an amino acid sequence having at least 30% amino acid sequence homology with the amino acid sequence of Cofilin (SEQ ID NO: 1), said Cofilin having the activity of promoting

growth and differentiation of hematopoietic stem cells, hematopoietic progenitors, or a combination thereof. The claims recite that the Cofilin is encoded by the base sequence depicted by SEQ ID NO: 2 or DNA comprising a base sequence having at least 30% base sequence homology with the base sequence of Cofilin depicted by SEQ ID NO: 2, said Cofilin having the activity of promoting growth and differentiation of hematopoietic stem cells, hematopoietic progenitors, or a combination thereof. The claims recite that the said promoter is for treating diseases that result from insufficient growth, differentiation of hematopoietic stem cells, hematopoietic progenitors. The claims recite that said promoter is for treating panhematopenia, diseases that are accompanied by hematopoietic hypofunction, or a combination thereof.

The specification teaches that isolated mouse bone marrow cells are incubated in culture with the human non-muscle type Cofilin protein of SEQ ID NO: 1 in amounts of 2500 ng/ml, 250 ng/ml, 25 ng/ml, and 2.5 ng/ml (pg 33, [107]). The specification at pg 33, [107-108] and Figure 4 indicate that at 6 and 10 days, the number of HPP-CFC colonies in the recombinant human nonmuscle-type Cofilin groups at concentrations of 2500 ng/ml, 250 ng/ml are significantly increased compared to control. Additionally, the specification of the instant application discloses that the human nonmuscle-type Cofilin in combination with SCF and FL caused cultured human umbilical cord blood derived CD34 positive cells to expand significantly as compared to control (pg 36, [116]; Figure 6A). Human nonmuscle-type Cofilin in combination with SCF and FL also caused an increase in the colony formation of CFU-GM (colony-forming unit granulocyte, macrophage), BFU-E (burst-forming unit erythroid), and CFU-Mix (colony-forming unit, mixed) as compared to controls (pg 36-37; Figure 6B-6D).

(i) However, the specification of the instant application does not teach the administration of any Cofilin to any subject for the promotion of growth and differentiation of hematopoietic stem cells or progenitor cells. The specification also does not teach the treatment any diseases that result from insufficient growth, differentiation of hematopoietic stem cells or hematopoietic progenitors comprising the administration of any Cofilin. For example, a large quantity of experimentation would be required by one skilled in the art to treat all possible diseases that result from insufficient growth and/or differentiation of hematopoietic stem cells and/or hematopoietic progenitors. Additionally, as was found in Ex parte Hitzeman, 9 USPQ2d 1821 (BPAI 1987), a single embodiment may provide broad enablement in cases involving predictable factors such as mechanical or electrical elements, but more will be required in cases that involve unpredictable factors such as most chemical reactions and physiological activity. See also In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970); Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991). The present invention is unpredictable and complex wherein one skilled in the art may not necessarily treat all diseases that result from insufficient growth and/or differentiation of hematopoietic stem cells and/or hematopoietic progenitors by administration of Cofilin. Significant further experimentation would be required of the skilled artisan to identify individuals with such a disease and to determine the route of administration of the Cofilin, as well as quantity and duration of treatment.

(ii) Furthermore, the specification of the instant application does not teach any methods or working examples wherein a subject is administered all possible Cofilin proteins. Undue experimentation would be required of the skilled artisan to administer all possible Cofilin

proteins to a subject. The specification also does not teach any method or working examples wherein hematopoietic stem cells are cultured with all possible Cofilin proteins. The specification discloses that "when the term 'Cofilin'' is used without any qualification in the present invention, it covers not only Cofilin having the amino acid sequence depicted by SEQ ID NO:1 but also its analogous compounds" (pg 11, lines 2-4). The specification also teaches that "the Cofilin as referred to in the invention include, for example, porcine destrin, chick actin depolymerizing factor (ADF), depactin from the egg of an urchin, yeast's Abpl, Acanthamoeba's actophorin, and their analogous compounds" (pg 13, [50]). Relevant literature teaches that there are at least twelve known mammalian Cofilins and that actin-depolymerizing factor (ADF)/Cofilins' most important physiological function is to depolymerize filaments from their pointed ends, thereby increasing actin dynamics (Vartiainen et al. Molec Biol Cell 13: 183-194, 2002; pg 183, 3rd full paragraph; pg 186, Figure 1B). However, the expression patterns and biochemical properties of mouse ADF/Cofilins are different. For example, Vartiainen et al. disclose that ADF is the most active ADF/Cofilin and is found in polarized epithelial and nervous tissues (pg 192, col 1, 2nd full paragraph). The muscle-specific Cofilin-2 has a weaker actin filament depolarization activity and displays a 5-10 fold higher affinity for ATP-actin monomers than ADF and Cofilin-1 (the non-muscle form) (pg 192, col 1, 1st full paragraph).. Therefore, based upon the art's disclosure of numerous Cofilin proteins and Cofilins' known activities and cell expression patterns, one skilled in the art would not predict that any Cofilin, except human non-muscle type Cofilin (as disclosed in the examples of the instant specification), would promote the growth or differentiation of hematopoietic stem cells and hematopoietic progenitor cells.

(iii) As discussed above, the specification of the instant application discloses that human non-muscle type Cofilin promotes the growth (proliferation) of hematopoietic stem cells and hematopoietic progenitor cells *in vitro/ex vivo* (pg 33, [107-108]). However, the specification does not teach that human non-muscle type Cofilin *alone* is able to promote the differentiation of hematopoietic stem cells or hematopoietic progenitor cells. In fact, Figures 6B-6D indicate that human nonmuscle-type Cofilin only in combination with SCF and FL or TPO causes an increase in the colony formation of CFU-GM (colony-forming unit granulocyte, macrophage), BFU-E (burst-forming unit erythroid), and CFU-Mix (colony-forming unit, mixed) as compared to controls. In these experiments, the Cofilin alone group is similar to the PBS and Input controls. Therefore, one skilled in the art would not be able to predict that Cofilin alone would promote the differentiation of hematopoietic stem cells or hematopoietic progenitor cells *in vivo*, *in vitro*, or *ex vivo*.

(iv) The specification of the instant application discloses that "Analogous compounds of Cofilin as referred to in the specification include the following which all have the activity of promoting the growth and/or differentiation of hematopoietic stem cells and/or hematopoietic progenitors: one comprising the amino acid sequence of Cofilin depicted by SEQ ID NO:1 except that it has one or more amino acid deletions, substitutions and/or additions; one comprising an amino acid sequence encoded by a base sequence hybridizable under stringent conditions with a base sequence complementary to the base sequence coding for the amino acid sequence of Cofilin depicted by SEQ ID NO:1; and one comprising an amino acid sequence having at least 30%, preferably at least 50%, more preferably at least 60%, and most preferably at least 70%, amino acid sequence homology with the amino acid sequence of Cofilin (SEQ ID

NO:1)" (pg 11, [44]). However, the specification does not teach any variant, fragment, or derivative of the human non-muscle type Cofilin protein other than the full-length amino acid sequence of SEQ ID NO: 1. The specification also does not teach functional and structural characteristics of the polypeptide variants, fragments, and derivatives recited in the claims.

The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, Biochemistry 29:8509-8517; Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further

experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone (Bork, 2000, Genome Research 10:398-400; Skolnick et al., 2000, Trends in Biotech. 18(1):34-39, especially p. 36 at Box 2; Doerks et al., 1998, Trends in Genetics 14:248-250; Smith et al., 1997, Nature Biotechnology 15:1222-1223; Brenner, 1999, Trends in Genetics 15:132-133; Bork et al., 1996, Trends in Genetics 12:425-427).

Due to the large quantity of experimentation necessary to treat all possible diseases that result from insufficient growth and differentiation of hematopoietic stem/progenitor cells comprising administering any Cofilin protein, to determine the optimal quantity, duration, and type of administration of Cofilin, and to generate the infinite number of derivatives recited in the claims and possibly screen same for activity; the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural and functional limitations and Cofilin protein limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

8. Claims 16-34 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are directed to a method of treating a disease or promoting growth, differentiation of hematopoietic stem cells, hematopoietic progenitor cells said method comprising administering at least one promoter of growth, differentiation of hematopoietic stem cells, hematopoietic progenitor cells, wherein said at least one promoter contains Cofilin as an active ingredient. The claims recite a method of regenerative medicine or expanding hematopoietic stem cells *ex vivo* by using at least one promoter of growth, differentiation of hematopoietic stem cells, hematopoietic progenitor cells, wherein said at least one promoter contains Cofilin as an active ingredient. The claims also recite that the Cofilin has the amino acid sequence depicted by SEQ ID NO: 1 or an amino acid sequence having at least 30% amino acid sequence homology with the amino acid sequence of Cofilin (SEQ ID NO: 1), said Cofilin having the activity of promoting growth and differentiation of hematopoietic stem cells, hematopoietic progenitors, or a combination thereof. The claims recite that the Cofilin is encoded by the base sequence depicted by SEQ ID NO: 2 or DNA comprising a base sequence having at least 30% base sequence homology with the base sequence of Cofilin depicted by SEQ ID NO: 2, said Cofilin having the activity of promoting growth and differentiation of hematopoietic stem cells, hematopoietic progenitors, or a combination thereof. The claims recite that the said promoter is for treating diseases that result from insufficient growth, differentiation

of hematopoietic stem cells, hematopoietic progenitors. The claims recite that said promoter is for treating panhematopenia, diseases that are accompanied by hematopoietic hypofunction, or a combination thereof.

The specification of the instant application discloses that "when the term 'Cofilin'' is used without any qualification in the present invention, it covers not only Cofilin having the amino acid sequence depicted by SEQ ID NO:1 but also its analogous compounds" (pg 11, lines 2-4). The specification continues to disclose that "analogous compounds of Cofilin as referred to in the specification include the following which all have the activity of promoting the growth and/or differentiation of hematopoietic stem cells and/or hematopoietic progenitors: one comprising the amino acid sequence of Cofilin depicted by SEQ ID NO:1 except that it has one or more amino acid deletions, substitutions and/or additions; one comprising an amino acid sequence encoded by a base sequence hybridizable under stringent conditions with a base sequence complementary to the base sequence coding for the amino acid sequence of Cofilin depicted by SEQ ID NO:1; and one comprising an amino acid sequence having at least 30%, preferably at least 50%, more preferably at least 60%, and most preferably at least 70%, amino acid sequence homology with the amino acid sequence of Cofilin (SEQ ID NO:1)" (pg 11, [44]).

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, there is not even identification of any particular portion of the Cofilin structure that must be conserved. Accordingly, in the

absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus. Additionally, the description of one polypeptide species (SEQ ID NO: 1) is not adequate written description of an entire genus of functionally equivalent polypeptides which incorporate all variants and fragments and with at least 30% sequence identity to the polypeptide comprising the amino acid sequence of SEQ ID NO: 1. Additionally, with regard to claims 22 and 24, simply reciting hybridization conditions in the claims does not yield adequate written description of the polynucleotides and polypeptides encompassed. The claims encompass an infinite number of polynucleotides that hybridize to the nucleic acid sequence of SEQ ID NO: 2. These polynucleotides may be structurally and functionally divergent from the polynucleotide of SEQ ID NO: 2.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed"* (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116).

With the exception of the sequences referred to above, the skilled artisan cannot envision the detailed chemical structure of the encompassed polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The polypeptide

itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only a human non-muscle type Cofilin comprising the amino acid sequence of SEQ ID NO: 1 or a human non-muscle type Cofilin encoded by the base sequence of SEQ ID NO: 2, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 16-34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

10. Claims 16-34 are indefinite because the claims do not have a step that clearly relates back to the preamble. For example, there is no step indicating that administration of Cofilin promotes growth, differentiation; treats a disease; expands hematopoietic stem cell *ex vivo*, etc.

11. Claims 18 and 32 are rejected as being indefinite because the metes and bounds of the phrase "combination thereof" cannot be determined. For example, it is not clear how a disease comprises a combination of panhematopenia and a disease that is accompanied by hematopoietic hypofunction. (It is noted that this issue could be overcome by amending the claims to remove recitation of ",or a combination thereof".)

12. Regarding claims 22, 24, stringency is relative, and the art does not recognize a single set of conditions as stringent. The specification also does not provide an unambiguous definition for the term. In the absence of a recitation of clear hybridization conditions (e.g., "hybridizes at wash conditions consisting of **A** X SSC and **B** % SDS at **C**°C"), the claims fail to define the metes and bounds of the varying structures of polynucleotides recited in the claimed methods.

13. Claims 28-31 recite the limitation "another cytokine" in line 1. There is insufficient antecedent basis for this limitation in the claim. Claims 28-31 depend from claims 16 and 17, which do not recite the term "cytokine".

14. Claims 19-20 and 34 provide for the use of "at least one promoter of growth, differentiation of hematopoietic stem cell, hematopoietic progenitors", but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

15. The term "regenerative medicine" in claims 20 and 34 is a relative term which renders the claims indefinite. The term "regenerative medicine" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the

art would not be reasonably apprised of the scope of the invention. It cannot be determined what method steps, products, and/or endpoints are encompassed by this phrase.

Conclusion

No claims are allowable.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure:

Konakahara et al. CD29 integrin- and LIMK1/cofilin-mediated actin reorganization regulates the migration of haematopoietic progenitor cells underneath bone marrow stromal cells. Genes Cells. 9(4):345-358, 2004.

Silva et al. The profile of gene expression of human marrow mesenchymal stem cells. Stem Cells. 21(6):661-669, 2003.

Nagaoka et al. Effects of cofilin on actin filamentous structures in cultured muscle cells. J Cell Sci. 108 (Pt 2):581-593, 1995.

Aizawa et al. Cofilin-2 is expressed at aggregation stage of Dictyostelium discoideum development. Genes Cells. 6(10):913-921, 2001.

WO 2004035092, treatment of inflammatory disease with agents which modulate expression of Cofilin

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (571) 272-0881. The examiner can normally be reached on 8:30-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

BEB
Art Unit 1647
01 June 2005

Bridget E. Bunner
patent examiner